Remarks

The Rejection of Claims 1-17 Under 35 U.S.C. § 112, first paragraph

Claims 1-17 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

Independent claim 1 is directed to a pair of cells. The cells are isogenic but for a gene of interest and a gene encoding a fluorescent protein. The Office Action asserts that the specification does not adequately describe the recited "gene of interest."

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). The specification need describe in detail, however, only that which is "new or not conventional in the art." M.P.E.P. § 2163(II)(A)(3)(a), citing *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). The present specification meets this standard.

The recited "gene of interest" is not a new element in the art. The use of this term in claim 1 merely reflects the fact that the claimed pair of isogenic cells can differ with respect to

any gene in which one practicing the invention is interested. By the September 21, 2001 filing date of the present application, many such genes were known in the art.

Nor is the recited "gene of interest" an unconventional element in the art. A search of the U.S. Patent and Trademark Office database for the term "gene of interest" in the claims identified 254 patents that use this term in a similar way. *See, e.g.*, U.S. Patent 6,413,717 filed March 18, 1998 (claim 1: " . . . contacting a cell comprising a gene of interest with a candidate agent under conditions and for a time sufficient to permit modulation of the level of mRNA transcribed from the gene of interest . . . ."); U.S. Patent 6,376,175 filed July 28, 1998 (claim 1: "A screening method to identify a chemical which transcriptionally modulates the expression of a gene-of-interest . . . ."); U.S. Patent 6,225,074 filed September 17, 1997 (claim 15: "A method of detecting the expression of a gene of interest by assaying for chloramphenicol acetyltransferase (CAT) present in a sample of a cell lysate due to expression of a CAT gene used as a reporter for measuring expression of a gene of interest in transfected cells . . . .).

The Office Action cites *Regents of the University of California v. Lilly* and *Enzo Biochem, Inc. v. Gen-Prove Inc.* to support the rejection. *Lilly* and *Enzo* addressed what is required for a written description of new genetic material. Applicants are not claiming a new "gene of interest" *per se*. Thus, the Office Action's reliance on *Lilly* and *Enzo* is misplaced.

The recited "gene of interest" is neither a new nor an unconventional element in the art. Applicants are not claiming a new gene *per se*. Thus, the specification need not describe the genus "genes of interest" in detail to support claims 1-17.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 1-17 Under 35 U.S.C. § 103(a)

Claims 1-17 stand rejected under 35 U.S.C. § 103(a) as obvious over Waldman, US 2002/0132340 ("Waldman") in view of Kain, *Drug Discovery Today 4*, 304-12, 1999 ("Kain"). Applicants respectfully traverse the rejection.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P., 8th ed., § 2142. In the present application, a *prima facie* case that claims 1-17 are obvious has not been made because the Office Action has not made a sufficient showing of a motivation to combine the teachings of the cited references.

The Office Action cites Waldman as teaching "a pair of isogenic cell lines comprising beta-catenin, wherein said cells are heterozygous for a wild-type and a mutant beta catenin gene, or hemizygous for wild-type beta-catenin, hemizygous for mutant beta-catenin, homozygous for wild-type beta catenin and homozygous for mutant beta-catenin." Office Action at page 6, first full paragraph. The Office Action cites Kain as teaching the use of combinations of fluorescent proteins to quantify mixed cell populations. Office Action at page 7, first full paragraph. The asserted motivation for combining these teachings is that Waldman "suggests the use of a fluorescent signal as a detectable phenotype." Office Action at page 7, second paragraph.

The asserted motivation is insufficient for one of ordinary skill in the art to have combined the cited references. The teachings of the cited references must be considered as a whole and compared with the subject matter of the rejected claims. *Graham v. John Deere* 383 U.S. 1, 17 (1966). In addition to the isolated teaching cited in the Office Action, Waldman discloses that the disclosed isogenic cell lines can be made by introducing a heterologous polynucleotide or recombinant nucleic acid molecule into the cell:

> [0045] A cell also can be genetically modified, for example, by introducing a heterologous polynucleotide or recombinant nucleic acid molecule into the cell such that the polynucleotide or nucleic acid molecule or a portion thereof is integrated into the genome of the cell. For example, a genetically modified cell can be a cell that has been treated according to a method of the invention such that both endogenous β-catenin genes have been knocked out, and has been further manipulated by introducing a polynucleotide encoding a wild type or an activated β-catenin polypeptide into the cell.

Waldman teaches that the introduced recombinant nucleic acid molecules can encode a reporter molecule or a selectable marker which can be used to generate a detectable phenotype; the detectable phenotype can then be used to determine whether the cell has integrated the recombinant nucleic acid molecule into its genome or to isolate and select cells that express the marker. See paragraphs [0048] and [0049]:

> [0048] Reporter molecules, which confer a detectable phenotype on a cell, are well known in the art and include, for example, fluorescent polypeptides such as green fluorescent protein, cyan fluorescent protein, red fluorescent protein, or enhanced forms thereof, an antibiotic resistance polypeptide such as puromycin N-acetyltransferase, hygromycin B phosphotransferase, neomycin (aminoglycoside) phosphotransferase, and the Sh ble gene product; a cell surface protein marker such as the cell surface protein marker neural cell adhesion molecule (N-CAM); an enzyme such as a β-lactamase, chloramphenicol acetyltransferase, adenosine deaminase, aminoglycoside phosphotransferase, dihydrofolate reductase, thymidine kinase, luciferase or xanthine guanine phosphoribosyltransferase polypeptide; or a peptide tag such as a

> c-myc peptide, a polyhistidine, a FLAG epitope, or any ligand (or cognate receptor), including any peptide epitope (or antibody, or antigen binding fragment thereof, that specifically binds the epitope; see, for example, Hopp et al., *BioTechnology* 6:1204 (1988); U.S. Pat. No. 5,011,912, each of which is incorporated herein by reference). Expression of a reporter molecule can be detected using the appropriate instrumentation or reagent, for example, by detecting fluorescence of a green fluorescent protein or light emission upon addition of luciferin to a luciferase reporter molecule, or by detecting binding of nickel ion to a polypeptide containing a polyhistidine tag. Similarly, expression of a selectable marker such as an antibiotic can be detected by identifying the presence of cells growing under the selective conditions.
>
> [0049] A reporter molecule also can provide a means of isolating or selecting a cell expressing the reporter molecule. For example, the reporter molecule can be a polypeptide that is expressed on a cell surface and that contains an operatively linked c-myc epitope; an anti-c-myc epitope antibody can be immobilized on a solid matrix; and cells, some of which express the tagged polypeptide, can be contacted with the matrix under conditions that allow selective binding of the antibody to the epitope. Unbound cells can be removed by washing the matrix, and bound cells, which express the reporter molecule, can be eluted and collected. Methods for detecting such reporter molecules and for isolating the molecules, or cells expressing the molecules, are well known to those in the art (see, for example, Hopp et al., supra, 1988; U.S. Pat. No. 5,011,912). As indicated above, a convenient means of isolating and selecting cells expressing a reporter molecule is provided by using a reporter molecule that confers antibiotic resistance, and isolating cells that grow in the presence of the particular antibiotic.

Waldman discusses methods of making the disclosed cell lines that use the disclosed phenotype selection. Paragraphs [0059]-[0062]. Waldman does not teach or suggest, however, two isogenic cell lines containing two different distinguishing molecules. In fact, Waldman defines a "set of isogenic cell lines" as "at least two separate populations of cells that are substantially genetically identical except for the nucleotide sequences of their β-catenin genes." Paragraph [0032], emphasis added. Because the populations of cells in the set of isogenic cell lines are separate, Waldman does not provide a motivation for modifying the cell lines to contain a gene

encoding a fluorescent protein "wherein the first cell comprises a gene that encodes a first fluorescent protein having a first absorption spectrum and a first emission spectrum; wherein the second cell comprises a gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum; and wherein either: the first and second absorption spectra are not identical; and/or the first and second emission spectra are not identical," as recited in independent claim 1.

Waldman also discloses "a method of using a set of isogenic cell lines to identify a therapeutic agent that allows selective killing of cells expressing an activated β-catenin polypeptide." Paragraph [0064]. The methods disclosed for identifying selective killing, however, do not involve detection of expression of different fluorescent proteins or other detectable markers from genes introduced into cells of the isogenic lines. Rather, Waldman teaches that:

> killing of cells can be examined, for example, using a vital stain such as trypan blue, which accumulates in dead cells, using a DNA binding dye such as propidium iodide or H33258 and examining the genomic DNA for a fragmentation characteristic of apoptosis, or measuring the incorporation of a labeled nucleoside such as tritiated thymidine or a nucleoside analog such as bromodeoxyuridine into the cellular DNA.

Paragraph [0064], internal reference omitted. Consistent with Waldman's definition of a set of isogenic cell lines as "separate populations," the disclosed methods do not distinguish between different cell types in a mixed population.

When Waldman is considered as a whole, Waldman's disclosure of use of a fluorescent protein as a phenotypic selection marker does not suggest a pair of isogenic cell lines that differ but for a gene of interest and "a gene encoding a fluorescent protein, wherein the first cell comprises a gene that encodes a first fluorescent protein having a first absorption spectrum and a

first emission spectrum; wherein the second cell comprises a gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum; and wherein either: the first and second absorption spectra are not identical; and/or the first and second emission spectra are not identical," as recited in independent claim 1. Waldman does not teach or suggest a mixed populations of cells and therefore does not teach or suggest a need to distinguish between populations of cells. Thus, at a minimum, the rejection should not apply to dependent claim 3, which recites that the first and second cells "are contained within the same undivided container" or to withdrawn claim 31, which recites that "the first and second cells are co-cultured."

Kain does not remedy the deficiencies of Waldman. Kain contains only a generic teaching that "various combinations of GFP spectral variants can be used to quantify mixed cell populations by flow cytometry." This teaching would not have been sufficient to have motivated one of ordinary skill in the art to have introduced genes encoding different fluorescent proteins into the cells of Waldman because Waldman does not teach mixed populations of cells.

There is, in fact, nothing in Waldman that would have pointed the ordinary artisan to the cited teaching in Kain. Nor would the cited teaching in Kain have caused the ordinary artisan to have introduced two different fluorescent proteins into members of Waldman's isogenic cell lines. The Patent and Trademark Office cannot pick and choose isolated elements of a reference and piece them together using Applicants' specification as a template:

> [s]tatements [in a prior art reference] cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no

> knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d (BNA) 1313, 1317 (Fed. Cir. 2000). Selecting isolated elements of the cited references is improper because it uses hindsight rather than considering the art from the viewpoint of the ordinary artisan at the time the present application was filed. *Id.* at 1369, 55 U.S.P.Q.2d (BNA) at 1316.

The Office Action has not established a sufficient motivation for the ordinary artisan to have combined the cited teachings of Waldman and Kain. Thus, there is no *prima facie* case of obviousness.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 1-3 and 11-20 Under 35 U.S.C. § 103(a)

Claims 1-3 and 11-20 stand rejected under 35 U.S.C. § 103(a) as obvious over Shirasawa *et al.*, *Science 260*, 85-88, 1993 ("Shirasawa") in view of Vande Woude *et al.*, U.S. Patent 5,645,988 ("Vande Woude") and Kain. Applicants respectfully traverse the rejection.

The Office Action cites Shirasawa as teaching isogenic cell lines that differ in alleles of K-Ras; it cites Vande Woude as teaching cancer cells that "differ as to the presence of a particular DNA sequence," including K-ras-2. Office Action at page 8, last paragraph, and page 9, first paragraph. The Office Action cites Kain as discussed above. The Office Action asserts it would have been obvious to combine these teachings "in order to use the color of the fluorescent protein as a detectable phenotype of the cell in order to measure the effects of toxic agent on cell [sic] which comprise the oncogenic Ras mutations as taught by Wander woude [sic] et al." Page 9, last paragraph.

As with the rejection over Waldman and Kain, discussed above, the Office Action has merely selected isolated teachings of each of the cited references and combined them using Applicants' specification as a guide. The teachings of the cited references, however, must be viewed as a whole. *Graham v. John Deere*, 383 U.S. at 17. When the entire teachings of the cited references are considered, there exists no legally sufficient motivation for one of ordinary skill in the art to have combined the cited teachings.

Shirasawa disrupted the activated Ki-*ras* genes in two cell lines, DLD-1 and HCT-116 "[t]o elucidate the role of Ki-*ras* in tumorigenesis." Abstract; page 85, col. 1, second paragraph. Shirasawa's experiments "suggest that the activated Ki-*ras* gene is directly responsible for the malignant phenotype of the DLD-1 and HCT 116 colon cancer cell lines." Page 87, col. 2, second paragraph. Shirasawa contains the following teaching of how the disclosed cell lines could be used in future studies:

> Thus, the use of these cell lines in studies of oncogene and tumor suppressor gene cooperation may help to elucidate further the molecular mechanisms that underlie colorectal tumorigenesis. The HR-M lines described here, which can be easily grown in vitro but show no tumorigenicity in nude mice, may also be useful for the investigation of other genetic alterations that are associated with the malignant phenotype.

Id. Shirasawa contains no teaching or suggestion that the disclosed cell lines could be used to screen for toxic agents or that it would be useful to incorporate a marker, such as a fluorescent protein, in the cell lines. Thus, Shirasawa contains no motivation to modify its teachings by combining them with those of either Vande Woude or Kain.

Vande Woude does not remedy the deficiencies of Shirasawa. Vande Woude, too, must be considered as a whole. *Graham v. John Deere*, 383 U.S. at 17. Vande Woude teaches that pairs of cell lines can be used to test the ability of antineoplastic drugs to selectively inhibit

cancer cell growth and discloses that some cell lines are more sensitive than others to tested drugs. *See, e.g.*, Example 3. Vande Woude contains no specific teaching of how antineoplastic drug sensitivity was or should be measured. Specifically, Vande Woude does not teach or suggest monitoring the effects of a drug on different cell types cells in a mixed population. Vande Woude teaches only detection of a "cellular response pattern" and "greater sensitivity" in such tests. *See* col. 43, lines 29-39:

> Similarly, exposure of the six cell lines to the nonsteroidal antiestrogen tamoxifen indicated a greater sensitivity of the KHOS-NP cell line to as [sic] compared with the parental HOS line. The cellular response pattern suggested a threshold for a drug concentration effective against these cells. Tamoxifen has been reported to inhibit protein kinase C in an intracellular transduction pathway (Suet al., *Biochem. Pharmacol.*, 34, 3649-3653 (1985); Horgan et al., *Biochem. Pharmacol.*, 35, 4463-4465 (1986)). The other four cell lines demonstrated intermediate sensitivity to bleomycin and tamoxifen as compared to the parental HOS cells.

Vande Woude does not teach mixed populations of cells and therefore does not teach or suggest a need to distinguish between members of a mixed cell population. Thus, this general disclosure is not sufficient to have motivated one of ordinary skill in the art to have introduced genes encoding different fluorescent proteins into members of the disclosed cell line pairs. Vande Woude in fact contains no specific teaching or suggestion that would have lead the ordinary artisan to make pairs of cell lines containing genes encoding different fluorescent proteins. Again, at a minimum, the rejection should not apply to dependent claim 3 or withdrawn claim 31.

Finally, as discussed above, Kain contains only a generic teaching that "various combinations of GFP spectral variants can be used to quantify mixed cell populations by flow cytometry." Because neither Shirasawa nor Vande Woude teaches mixed cell populations or a

need to distinguish between different cell types in a mixed cell population, this teaching would not have been sufficient to have motivated one of ordinary skill in the art to have prepared a pair of isogenic cells that differ but for a gene of interest and a gene encoding a fluorescent protein, "wherein the first cell comprises a gene that encodes a first fluorescent protein having a first absorption spectrum and a first emission spectrum; wherein the second cell comprises a gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum; and wherein either: the first and second absorption spectra are not identical; and/or the first and second emission spectra are not identical.," as recited in independent claim 1.

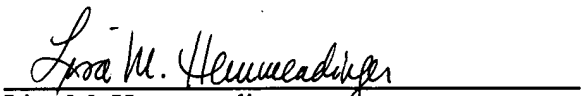
It is improper to use Applicants' specification as a lens through which to view the prior art. *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998) ("the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed"). The claimed pair of isogenic cells is disclosed only in Applicants' specification and is not suggested by the cited art.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Date: May 20, 2004

By: 

Lisa M. Hemmendinger
Registration No. 42,653

Customer No. 22907